



Ambler, G. K., Coughlin, P. A., Hayes, P. D., Varty, K., Gohel, M. S., & Boyle, J. R. (2015). Incidence and Outcomes of Severe Renal Impairment Following Ruptured Abdominal Aortic Aneurysm Repair. *European Journal of Vascular and Endovascular Surgery*, 50(4), 443-449. <https://doi.org/10.1016/j.ejvs.2015.06.024>

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# Incidence and Outcomes of Severe Renal Impairment Following Ruptured Abdominal Aortic Aneurysm Repair

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## WHAT THIS PAPER ADDS

Acute kidney injury (AKI) is common following ruptured abdominal aortic aneurysm repair. The incidence of AKI is higher after open repair than after endovascular repair, allaying previous concerns about the risk of contrast nephropathy in these patients, and is associated with the level of aortic clamping during open repair. Patients who experience significant AKI suffer worse outcomes, so identification of high-risk patients may lead to improved patient outcomes from renal specific interventions in the peri- and early postoperative period.

**Introduction:** Acute kidney injury (AKI) following ruptured abdominal aortic aneurysm (rAAA) repair is common and multifactorial. A standard definition of AKI after endovascular repair (EVAR), the Aneurysm Renal Injury Score (ARIS<sub>e</sub>), has been proposed to facilitate standardised reporting and thus improve understanding of this issue.

**Methods:** Data were collected retrospectively on AKI in a prospectively maintained database of all patients treated for rAAA in a single tertiary referral centre since the availability of routine out of hours emergency EVAR. The ARIS<sub>e</sub> score was used to describe the degree of AKI and factors which correlated with poor renal outcomes were assessed.

**Results:** Two-hundred and five patients were treated between January 2006 and April 2014. Of these, 125 were treated with open repair (OSR) and 80 were treated with EVAR. Severe AKI (defined as ARIS<sub>e</sub> score  $\geq 3$ ) occurred in 36% of patients. After correction for confounders, patients treated with OSR were significantly more likely to develop severe AKI (43% vs. 26%,  $p = .02$ ). There was no significant difference in preoperative serum creatinine between groups, but increased preoperative serum creatinine was strongly associated with severe AKI postoperatively ( $p < .001$ ). Age, sex, endograft type, and preoperative CT scanning were not associated with differences in renal outcomes. Clamp position above renal arteries was predictive of severe AKI in patients treated with OSR ( $p < .01$ ). Patients suffering severe AKI had significantly higher mortality at 30 days and 12 months (28% vs. 5% and 44% vs. 13%,  $p < .001$  for both comparisons).

**Conclusion:** Severe AKI is common following successful repair of rAAA. In this large case series of high-risk patients, OSR was associated with significantly higher rates of severe AKI compared with EVAR, despite the increased dose of contrast involved in EVAR and the older age of these patients. In turn, severe AKI was associated with higher mortality rates.

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Article history: Received 4 September 2014, Accepted 1 June 2015, Available online 15 July 2015

**Keywords:** Aortic aneurysm, Abdominal, Acute kidney injury, Survival analysis

## INTRODUCTION

Recent advances in the treatment of abdominal aortic aneurysm (AAA) have led to significant improvements in short-term mortality for elective repair, which has fallen to around 2% in real world series.<sup>1</sup> While outcomes following ruptured AAA (rAAA) have also improved,<sup>2</sup> mortality

remains around 30% in modern series.<sup>3–5</sup> One of the major causes of short-term mortality is the multiple organ dysfunction syndrome (MODS),<sup>6,7</sup> with AKI being particularly common.<sup>8</sup> In turn, AKI increases longer-term cardiovascular risk and chronic kidney disease.<sup>9</sup>

AKI in the context of rAAA repair has a multifactorial aetiology, with contributions arising from prolonged hypovolaemia, acute-on-chronic disease related to pre-existing renovascular or other kidney disease, and contrast-induced nephropathy in most patients, along with the deliberate sacrifice of accessory renal arteries arising from the aneurysm sac in some patients, although this latter factor was not shown to have a significant impact on chronic kidney disease after elective EVAR.<sup>10</sup> In addition, those undergoing open repair (OSR) may have additional

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<http://dx.doi.org/10.1016/j.ejvs.2015.06.024>

risk associated with supra-renal aortic clamping, while those undergoing endovascular repair (EVAR) are likely to have a significantly higher contrast load.

One of the problems with the current literature on AKI following AAA repair is the lack of a consensus on the way it is reported.<sup>11</sup> Some authors report serum creatinine values, some use modern categorisations such as the RIFLE (Risk, Injury, Failure, Loss, End-stage) classification,<sup>12</sup> some simply report the requirement for temporary or permanent renal replacement therapy. This plethora of different endpoints makes reading confusing and attempts at meta-analysis challenging. Recently, Twine et al. proposed a standard definition: the ARiSe (Aneurysm Renal Injury Score) classification (Table 1),<sup>11</sup> which is based on the RIFLE classification but tailored towards aneurysm repair. Although they proposed its use in the context of endovascular repair, it is equally applicable to open surgery.

The aim of this study was to investigate the incidence of AKI using the ARiSe classification at the study centre, and the impact of AKI on short- and longer-term mortality and length of stay.

## METHOD

### Study population

All patients treated at Addenbrookes Hospital for ruptured abdominal aortic aneurysm during the period January 1, 2006 until April 30, 2014 were included in the study. The study period was chosen as it reflects the period following the routine availability of out of hours emergency EVAR. Follow-up was until July 2014. All patients were assessed emergently by a consultant vascular surgeon and a decision was made with regard to suitability for OSR or EVAR based on patient factors (including haemodynamic stability) and anatomical suitability, although no formal scoring system or protocol was employed. Patients were selected for operative or non-operative treatment on clinical grounds at the discretion of the treating surgeon. The operative team for an EVAR consisted of a consultant vascular surgeon and a consultant interventional radiologist and the EVAR was performed in a standard operating theatre with a C arm. Niopam 300 contrast was used for angiography in all EVAR cases. The team for OSR consisted of a consultant vascular surgeon and a senior general or vascular surgical trainee. An anaesthetist (senior trainee or consultant grade) was also

present even for cases performed under local anaesthetic. Immediate postoperative care was either in a high dependency area or the intensive care unit depending on clinical need, with step down to ward care as clinically appropriate. Data on treatment for ruptured AAA in the unit have been reported previously, including patients from the earlier portion of the study period,<sup>5,13</sup> but renal outcomes have not been discussed previously. Data were collected as part of routine service evaluation and no patient-identifiable data are presented, so it was not deemed necessary to seek ethical approval or retrospective consent for the study.

### Data collected

The patient database has been prospectively maintained since January 2006, including basic patient demographics, comorbidity, medication history, length of stay, and mode of repair. Further retrospective case note review was performed to gather details of preoperative and intraoperative haemodynamics (lowest systolic blood pressure and highest pulse rate recorded prior to induction of anaesthesia and after induction of anaesthesia or instillation of local anaesthetic for those patients treated without general anaesthesia), as well as renal outcomes and contrast volumes where available for those patients treated with EVAR. Contrast doses largely reflect the amount opened (in 50 mL vials) rather than the amount which was actually used, as the amount actually injected has only recently started to be recorded. AKI rates were assessed in those patients surviving for at least 24 hours following surgery, as it was felt that it was not possible to accurately assess renal function in those surviving for less than 24 hours. AKI was defined as 'severe' if the patient suffered ARiSe category  $\geq 3$  AKI. The subset of these patients who required temporary or permanent renal replacement therapy was also examined.

An important issue when attempting to fulfil this aim relates to adjustment for preoperative renal function in these patients. Clearly, it would be optimal if glomerular filtration rate (GFR) could be assessed, or at least estimated GFR (eGFR) in the preoperative phase. However, few patients presenting with rAAA have had this assessed previously, and the use of formulae to calculate eGFR is specifically recommended against by nephrology associations in the acute setting when serum creatinine is unlikely to be stable, as these formulae were not developed for this purpose and have never been validated in this setting.<sup>14</sup> Therefore, we elected to perform rigorous confounder adjustment by way of appropriate multivariate models, incorporating serum creatinine, demographic data, and comorbidities separately rather than attempting to adjust for eGFR, which cannot be assessed reliably for most patients.

Mortality data were updated using the hospital electronic medical records system, which is linked to the United Kingdom Office for National Statistics.

To investigate the effects of clamp site on acute kidney injury, mortality, and length of stay in patients treated with OSR, a simple scoring system was introduced, the Level Of

**Table 1.** Aneurysm Renal Injury Score (ARiSe) classification.<sup>11</sup>

Score	Definition
1	Rise in serum creatinine $> 26 \mu\text{mol/L}$ but $< 50\%$ increase from baseline or urine output $< 0.5 \text{ mL/kg/h}$ for 6 hours within 7 days
2	Rise in baseline serum creatinine 50–99% within 7 days
3	Rise in baseline serum creatinine $\geq 100\%$ within 7 days
4	Requirement for temporary renal replacement therapy
5	Permanent renal replacement therapy

Clamp (LOC) score, with zero points for an infra-renal clamp, 1 point for a trans-renal clamp, 2 points for a supra-renal clamp, and 3 points for a clamp placed above either the superior mesenteric or coeliac artery. This integer score allowed examination of whether there was an incremental difference in outcomes as the LOC increased. It was also recorded whether the clamp was positioned at this level only initially to gain control of bleeding during dissection, or whether the clamp was positioned at this level while the anastomosis was being sewn. Clamp position during anastomosis was also used as a surrogate for whether an aneurysm was infra-renal, and sensitivity analysis was performed to look at whether comparisons between open and endovascular repair were robust to the exclusion of patients with a LOC score greater than zero. Division of the left renal vein was also recorded, as was whether a tube graft or a more complicated graft was used.

### Statistical analysis

Statistical analysis was performed using the R statistical package version 3.1.1 together with the “survival” add-on package. Fisher’s exact test was used to compare contingency data, while the Mann–Whitney *U* test was used to assess the significance of differences in continuous variables between groups. The log rank test was used to test for survival differences, and Cox proportional hazards modelling was used to adjust for confounders (age, gender, preoperative creatinine, history of ischaemic heart disease, stroke/TIA, or diabetes, preoperative use of  $\beta$ -blockers or statins, preoperative blood pressure and heart rate) in terms of survival, while Poisson regression was used for this adjustment when assessing for differences in length of stay and logistic regression modelling was used when assessing for differences in the incidence of severe AKI or requirement for renal replacement therapy. Cases with relevant missing data were excluded from multivariate analysis.

## RESULTS

Two-hundred and fifty-five patients were treated for rAAA between January 2006 and April 2014, of whom 205 were treated operatively and 50 (19.6%) were palliated. One-hundred and twenty-five were treated with OSR, whereas

80 were treated with EVAR. Median follow-up for patients surviving to the end of the study was 50 months (IQR 23–74 months). Patients treated with EVAR were older than those treated with OSR (median age 78 vs. 75 years, respectively,  $p = .046$ ) and more likely to have a history of ischaemic heart disease (47% vs. 32%,  $p = .038$ ), but otherwise demographics, comorbidities and preoperative medications were similar between these two groups (Table 2). In particular, there was no significant difference in preoperative creatinine between these groups ( $p = .62$ ). Patients treated with OSR had median lowest preoperative systolic blood pressure of 80 mmHg (IQR 65–107), compared with a median lowest preoperative systolic blood pressure of 100 mmHg (IQR 81–124) in the EVAR group. This difference was statistically significant ( $p < .001$ ).

### Acute kidney injury

None of the patients treated had received renal replacement therapy prior to presentation. Severe AKI (defined above as ARISe category  $\geq 3$  AKI) occurred in 67 (36%) of the 186 patients who survived for at least 24 hours following surgery. Percentages below of patients suffering severe AKI or requiring renal replacement therapy are therefore based on a total of 186 patients rather than the original 205. Fifty-four of these required temporary renal replacement therapy. Only three patients (one in the OSR group, two in the EVAR group) went on to require permanent renal replacement therapy during the follow-up period of the study. Significantly more patients treated with OSR suffered severe AKI than those treated with EVAR (43% versus 26%, respectively,  $p = .02$ ). These differences remained significant after adjusting for confounders ( $p = .02$ ), including measures of haemodynamic instability. Patients treated with OSR also had a higher requirement for temporary or permanent renal replacement therapy, although this difference was not statistically significant (36% vs. 23%, adjusted  $p = .12$ ).

Other than the type of repair, the only significant predictor of severe AKI was preoperative serum creatinine (median [IQR] preoperative serum creatinine for those patients not suffering severe AKI: 121 [98–158]  $\mu\text{mol} \cdot \text{L}^{-1}$  vs. 147 [118–187]  $\mu\text{mol} \cdot \text{L}^{-1}$  in those suffering severe AKI;

**Table 2.** Demographics, comorbidities, and preoperative medications for patients treated by OSR or EVAR.

Parameter	OSR	EVAR	<i>p</i>
Age, median (IQR)	75 (69–81)	78 (73–82)	.046
Male (%)	111 (88)	66 (83)	.22
Lowest preoperative systolic blood pressure: median (IQR), mmHg	80 (65–107)	100 (81–124)	$8 \times 10^{-5}$
Highest preoperative pulse rate: median (IQR), bpm	85 (70–105)	81 (70–95)	.07
Preop creatinine: median (IQR), $\mu\text{mol} \cdot \text{L}^{-1}$	135 (110–173)	129 (107–167)	.62
Previous ischaemic heart disease (%)	40 (32)	37 (47)	.038
Previous stroke/TIA (%)	9 (7)	8 (10)	.60
Pre-existing diabetes mellitus (%)	9 (7)	6 (8)	1.0
Preoperative $\beta$ -blocker use (%)	25 (20)	21 (27)	.31
Preoperative statin use (%)	60 (48)	37 (47)	.89

TIA = transient ischaemic attack.

$p < .001$ ). The adjusted odds ratio of severe AKI predicted by the median difference in serum creatinine of  $26 \mu\text{mol L}^{-1}$  was 1.34 (95% CI 1.14–1.59). Ninety-three (74%) patients treated with OSR had a preoperative CT scan. There was no significant increase in the rate of severe AKI in these patients (45% vs. 37%,  $p = 0.39$ ). Data on contrast volume used during EVAR were available for 60 of the 74 patients treated with EVAR who survived at least 24 hours. The median (IQR) contrast volume used was 200 (136–270) mL. EVAR patients suffering severe AKI had a higher median volume of contrast used, but this difference did not reach statistical significance (median [IQR] volumes for patients with and without severe AKI 270 [158–300] mL and 200 [130–250] mL, respectively,  $p = .10$ ).

When patients in the OSR group with LOC score greater than zero were excluded from analysis, the difference in incidence of severe AKI between OSR and EVAR groups was no longer significant (37% vs. 26%, adjusted  $p = .25$ ).

### Mortality

Overall 30-day mortality was 21.5%, which increased to 30.9% at 12 months. There were no significant differences in unadjusted survival between those treated with EVAR and those treated with OSR at any time point. After adjustment for the confounders age, gender, comorbidities, and preoperative creatinine, however, there was a significant 30-day survival advantage for those treated with EVAR over those treated with OSR (16.2% in the EVAR group versus 24.8%; hazard ratio 2.2, 95% CI 1.1–4.6,  $p = .03$ ), although this had disappeared by 12 months (28.8% compared with 32.2% in the OSR group; hazard ratio 1.4, 95% CI 0.8–2.5,  $p = .20$ ). When preoperative haemodynamic variables were included in the confounder adjustment model, even the small early survival benefit of EVAR disappeared. Kaplan–Meier survival curves are shown in Fig. 1.

Patients suffering severe AKI or requiring renal replacement therapy had significantly higher mortality at 30 days, 12 months, and overall (Table 3, Fig. 2;  $p < .001$  for all comparisons).

### Length of stay

The median length of stay in the study cohort was 12 days (IQR 6–25 days). This was significantly longer in the OSR group (median 14 days, IQR 7–27 days) than the EVAR group (median 8.5 days, IQR 5–16.5 days,  $p < 0.01$ ). Patients suffering severe AKI or requiring renal replacement therapy had significantly prolonged length of stay, independent of which type of repair was performed (Table 3;  $p < .001$  for both comparisons). The effects of operation and AKI on length of stay persisted after adjustment for confounders, including haemodynamic instability ( $p < .001$ ).

### Clamp level in the OSR group

In the subgroup treated with OSR, clamp site was recorded in 123/125 cases. A supra-coeliac clamp (LOC score = 3) was used initially in 43 cases (35%), but in all but five of

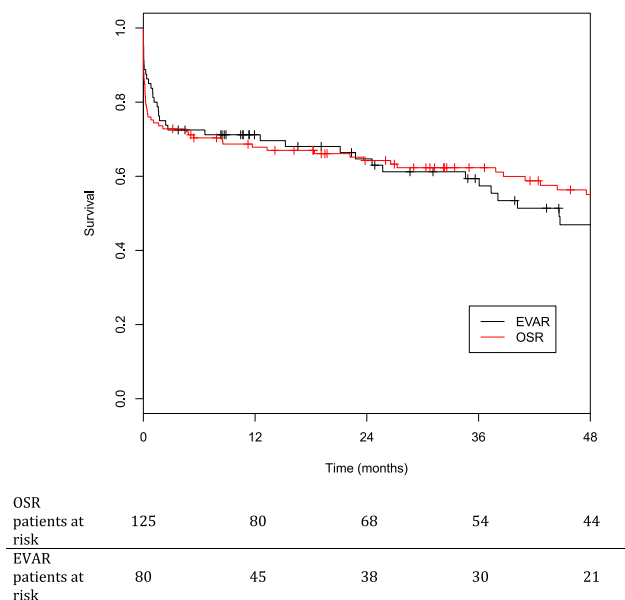


Figure 1. Survival following repair of rAAA by operation.

these cases this initial clamp was moved to a lower level following dissection. In 94 cases the clamp during anastomosis was infra-renal (LOC score = 0), in nine cases it was trans-renal (LOC score = 1) and in 15 cases it was supra-renal (LOC score = 2). A more proximal clamp position (higher LOC score) during anastomosis was significantly associated with adverse outcome, including increased mortality at 30 days ( $p = .01$ ) and 12 months ( $p = .03$ ); an increased risk of severe AKI ( $p < .01$ ); and prolonged length of stay ( $p < 0.001$ ) after correction for confounders. This was especially apparent in the small group of patients who required a supra-coeliac clamp during anastomosis, none of whom survived more than 24 hours. In contrast, the level of initial clamping was not predictive of either mortality or severe acute kidney injury. Data comparing LOC score during anastomosis with the incidence of severe AKI and the need for RRT are presented in Table 4. Correcting for LOC score during anastomosis did not alter the association between severe AKI and survival or prolonged length of stay. Division of the left renal vein and graft type (tube or otherwise) were not associated with outcome.

### DISCUSSION

This study has shown that severe AKI is common following rAAA repair, affecting over a third of patients who survived the first 24 hours from the cohort, which includes renal outcomes from the largest cohort of rAAA patients treated endovascularly in the literature to date. AKI was more common in patients undergoing OSR than it was in patients treated endovascularly, despite the substantial increase in contrast load in these patients, suggesting that contrast nephropathy is not a major cause of renal dysfunction in this cohort. This is in sharp contrast to early work on endovascular repair of rAAA, where small studies showed significantly worse renal outcomes in patients treated with EVAR.<sup>15</sup> This difference persisted when patients treated



**Table 3.** Effect of severe AKI or requirement for RRT (renal replacement therapy) on mortality and length of stay.

Outcome	ARISe < 3	Severe AKI (ARISe 3–5)	RRT	p (severe AKI)	p (RRT)
30-day mortality (%)	5	28	33	<.001	<.001
12-month mortality	13	44	52	<.001	<.001
Length of stay: median (IQR)	10 (7–18)	26 (13–40)	25 (11–44)	<.001	<.001

with OSR with a higher LOC score during anastomosis were excluded, although the difference was no longer statistically significant. Perhaps unsurprisingly, patients suffering from AKI experienced substantially longer hospital stays and higher 30-day and 12-month mortality rates.

The issue of AKI after rAAA repair was recently studied in a large Dutch series<sup>16</sup> consisting mainly of patients treated with OSR, and using the RIFLE<sup>12</sup> classification. Similar to the present study, they found AKI to be common after rAAA repair, and that those suffering from AKI suffered a higher in-hospital/30-day mortality rate. This reinforced previous work from smaller series before the endovascular era.<sup>17,18</sup>

The present work complements much previous work on AKI after elective AAA repair<sup>19</sup> and, together with the Dutch study referred to above, strongly refutes the preconception that contrast nephropathy is a significant concern following EVAR.

Results of the recent AJAX trial<sup>4</sup> were also broadly similar, although this trial has been criticised for the small number of patients recruited, the long time period of recruitment, and the small percentage of screened patients who were deemed “suitable.”<sup>20</sup>

After adjusting for confounders, a significant benefit of EVAR over OSR was found in terms of 30-day mortality, although this disappeared at later time-points and after adjustment for haemodynamic instability. This is in contrast with the findings of both the AJAX trial<sup>4</sup> and the much larger IMPROVE trial,<sup>3</sup> which both found no significant short-term benefit of an endovascular strategy. It is

interesting to note that this difference disappeared once haemodynamic parameters were taken into account, implying that this may be a significant confounder in previous case series which found in favour of an endovascular strategy. One major benefit of randomised studies is that the randomisation process corrects for unmeasured confounders, so it is possible that this difference simply reflects incomplete confounder adjustment. Few data are currently available on renal outcomes in the IMPROVE trial population. It would be interesting to compare the present results with this randomised population.

This centre did participate in the IMPROVE trial, which took place during part of the data collection period; however, only 33 of the 205 patients presented here were randomised within the trial, so small differences in the management of these patients compared with other patients in the study are unlikely to have a significant impact on the overall results.

In the elective setting, level of aortic clamping has previously been shown to adversely affect renal outcome in small case series.<sup>21</sup> The present study confirms this finding in the emergent setting, although it is interesting that the use of a higher level clamp to gain control during dissection did not have a significant adverse impact on any of the outcomes studied, implying that the use of this manoeuvre to gain control during dissection is safe. The association of a higher level of clamping with worse outcomes is also concordant with recently presented data from the IMPROVE trial, which suggests that infra-renal neck length may influence outcomes in both open and endovascular patients (personal communication).

The major strengths of the work include the size of the database, which includes the largest cohort of acute renal outcomes in patients treated endovascularly for rAAA in the literature, the fact that the database has been prospectively maintained and rigorously interrogated against the hospital coding system to reduce the degree of recall bias, and the length of follow-up, with a substantial proportion satisfying the British Society of Endovascular Therapy reporting standards definition of “long term.”<sup>22</sup>

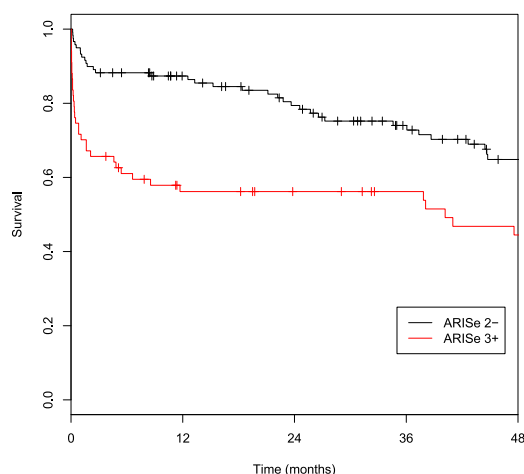
**Table 4.** Effect of aortic clamp level on acute renal outcomes.

LOC score during anastomosis	Number of patients	Incidence of severe AKI (%)	Need for RRT (%)
0 (infra-renal)	94	37	30
1 (trans-renal)	9	44	44
2 (supra-renal)	15	80	64
3 (higher level clamp)	5	-	-

LOC = Level Of Clamp.

Percentages in columns 3 and 4 are based on the 112 patients treated with OSR who survived at least 24 hours.

No patients with LOC score = 3 survived 24 hours.

**Figure 2.** Survival following repair of rAAA according to degree of AKI. ARISe: Aneurysm Renal Injury Score.

Weaknesses include some data on the patients being collected from retrospective review of medical notes, although the list of patients was maintained prospectively. A further weakness is that mortality data rely somewhat on the peculiarities of the death certification system in England and Wales, which has come under recent criticism as there can occasionally be some time lag between the death of a patient and certification, as certificates are only issued after the cause of death has been established.<sup>23</sup> Finally, no adjustments were made for anatomic confounders as a reasonable proportion of the patients in the OSR group had no preoperative CT scan. Given previous reports of favourable outcomes even for patients treated with OSR if they are suitable for EVAR, this effect may be significant.<sup>24</sup>

Given the high rates of severe AKI identified in this and other studies looking at patients following rAAA repair and the poor outcomes of these patients, it is natural to suggest that perhaps early renal replacement therapy might be beneficial in this cohort. There has been some work in patients following cardiac surgery which suggests that this may indeed be an important intervention,<sup>25</sup> and a randomised controlled trial is under way to investigate this question in patients with septic shock.<sup>26</sup> Given the high incidence of SIRS following rAAA repair,<sup>7</sup> the results of this trial may be transferrable to rAAA patients, but a randomised trial of early versus delayed renal replacement therapy in patients treated for rAAA would provide the best evidence.

In conclusion, severe AKI is common in all patients following repair of rAAA, but the endovascular treatment of rAAA patients, when feasible, results in a lower incidence of severe AKI despite administration of contrast medium. Patients suffering severe AKI have significantly prolonged lengths of stay and reduced short- and long-term survival. Further work is needed to determine whether this high-risk cohort would benefit from early renal replacement therapy.

## CONFLICT OF INTEREST

None.

## FUNDING

GKA received funding as an Academic Clinical Fellow from the UK National Institute for Health Research (1456).

## ACKNOWLEDGEMENTS

The authors would like to thank H. Lee and N. Al-Zuhir for their assistance in checking the completeness of the database, J. Shak and K. Reid for their help in collecting some of the data, and C. Cousins, A. Winterbottom, T.C. See, B. Koo, and M. Krokidis who contributed to the management of these patients.

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